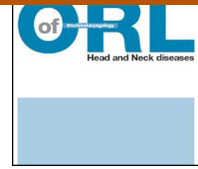




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REVIEW

Vestibular schwannoma and cell-phones. Results, limits and perspectives of clinical studies

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KEYWORDS

Vestibular schwannoma;
Cellular phone;
Electromagnetic fields

Summary The widespread development of cell-phones entails novel user exposure to electromagnetic fields. Health impact is a public health issue and a source of anxiety in the population. Some clinical studies reported an association between cell and cordless phone use and vestibular schwannoma; others found none. A systematic review was performed of all published clinical studies (cohort, registry, case-control and validation studies), with analysis of results, to determine the nature of the association and the level of evidence. Cohort studies were inconclusive due to short exposure durations and poor representativeness. Registry studies showed no correlation between evolution of cell-phone use and incidence of vestibular schwannoma. Case-control studies reported contradictory results, with methodological flaws. Only a small number of subjects were included in long-term studies (> 10 years), and these failed to demonstrate any indisputable causal relationship. Exposure assessment methods were debatable, and long-term assessment was lacking. An on-going prospective study should determine any major effect of electromagnetic fields; schwannoma being a rare pathology, absence of association will be difficult to prove. No clinical association has been demonstrated between cell and cordless phone use and vestibular schwannoma. Existing studies are limited by their retrospective assessment of exposure.

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Introduction

Ionizing radiation is presently the one established oncogenic factor in sporadic vestibular schwannoma [1,2]. Other factors, however, are discussed, including electromagnetic field exposure.

Cell-phones and cordless phones, which release an electromagnetic field close to the head, might be oncogenic and are a source of public health concern. Their use has

increased exponentially over the last 10 years: according to the International Telecommunication Union, 4 billion subscriptions had been taken out by the end of 2008, representing 60% of the world population; there were 61.4 million subscriptions in France in 2009, concerning 95.8% of the population, 71% of 12- to 14-year-old and 95% of 15- to 17-year-old [3,4]. In the discussion, inflaming a society still under the trauma of recent health scandals, expert opinions struggle to defend either a scientific hypothesis or powerful economic lobbies (protection against electromagnetic fields, cell-phone network operators...).

The present critical analysis of the literature addresses the question as to whether there exists an association

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between cell and cordless phone use and sporadic forms of vestibular schwannoma.

Material and method

A systematic review was undertaken of the French and international scientific literature on cell and cordless phone use and vestibular schwannoma, using the PubMed (www.ncbi.nlm.nih.gov) and Cochrane (<http://www.cochrane.org/>) databases. Four categories of keywords were defined and crossed, based on the MeSH Database:

- pathology: neoplasms, nervous system neoplasms, acoustic neuroma;
- intervention factor: cellular phone, telecommunication;
- type of study: case-control studies, meta-analyses, registries;
- and methodological limitations: bias, mental recall.

The searches of PubMed and Cochrane retrieved 42 references, from which studies were categorized by type: two cohort studies [5,6]; four registry studies [7–10]; 23 articles on case-control studies [11–34]; five meta-analyses [35–39]; and eight validation studies [40–47].

Each report was assessed in terms of type of study, sample size, group homogeneity, and quality of description of intervention factor exposure (notably, durations and intervals).

Conflicts of interest were also examined, in terms of declared financing of research.

Results

Cohort studies

The study by Johansen et al. [5] included 450,000 Danish cell and cordless phone users (including 150,000 analogic phone users), and failed to find an association between cell-phone use and vestibular schwannoma.

The study had numerous limitations. Exposure time was short: less than 4 years for 92% of users and less than 2 years for 69%. Mean follow-up was only 3.1 years. Exposure was approximated from the number of years' subscription according to the contracts, rather than the cumulative duration of calls. Corporate subscriptions were not included, resulting in 200,000 out of 723,000 subscribers being excluded. Only private calls were thus taken into account, to the exclusion of intensive business use. Finally, there existed a conflict of interest, the study being financed by telecoms operators.

Rothman et al.'s cohort study (1996) [6] likewise found no excess mortality in cell-phone users; the methodological limitations, however, were also similar.

Registry studies

Nelson et al. [7] used the national cancer registries of England and of Wales to inventory acoustic neuroma for the period 1979–2001. They reported increased incidence, in

line with American [8] and Danish studies [9]. For the period 1990–1997, the increase mainly consisted in the discovery of small intra-canal neuromas by new diagnostic imaging techniques (CT and MRI), and the fall in incidence after 1997 may have been due to exhaustion of this "reserve" of infraclinical neuromas.

Inskip et al. [10], in a more recent registry study for the period 1992–2006, found no correlation between the evolution of cerebral tumor and of cell-phone use.

Case-control studies

Two types of case-control study are to be distinguished: early clinical studies with small samples and short follow-up, and the INTERPHONE study and those by Hardell et al., which had larger study populations and longer follow-up.

First clinical studies

Muscat et al.'s case control study [11,12] included 90 patients and 86 controls. Relative risk was 0.9 ($p=0.07$), with no significant variation according to frequency, duration or cumulative time of cell-phone use. Tumors were mainly contralateral to the usual side of phone-use.

Duration of use, however, was less than 6 years, and less than 2 years in 90% of cases. Ninety-seven percent of the study population had less than 60 hours' cumulative exposure per year. The small sample and short exposure prevented ruling out an association.

Inskip et al. [13] compared 96 brain tumor cases to a control group of 799 hospital patients. Relative risk on odds ratio was 1.4 with 95% confidence intervals of 0.6 and 3.5. No correlation was found between side of phone-use and tumor side ($RR=0.9$; $p=0.63$).

The study involved several limitations. Using hospital patients as controls impaired representativeness. Cell-phone use among those who were users was low, with few (22 out of 96) regular users and only five with at least 5 years' use. Finally, side of phone-use and tumor side was analyzed on a very small sample: 14 patients with at least 6 months' exposure.

The INTERPHONE and Hardell et al. studies

The international INTERPHONE study [14–21] recruited several teams, coordinated by the International Agency for Research on Cancer, with a common basic protocol [22]. Data were collected by interview in hospital shortly after diagnosis.

Hardell et al. [23–34] studied 130 cases and 900 controls over a 6-year period from 1997 to 2003. Data were collected by mail 2 months after surgery. The study had the originality of including cordless phone use and of distinguishing between 1st and 2nd generation cell-phones. A questionnaire was used to limit interpretation and suggestion bias. The response rate was very high (about 90% for cases and controls), ensuring representativeness.

These studies had divergent findings.

None of the INTERPHONE studies reported an association between cell-phone use and vestibular schwannoma (Table 1). Schoemaker et al. [14] reported results from most of the countries involved in the study.

Table 1 Synopsis of INTERPHONE studies.

Study	Country	<i>n</i> cases	<i>n</i> controls	OR	Confidence interval
Lönn et al. 2004 [16]	Sweden	89	356	0.8	0.5–1.4
Christensen et al., 2004 [15]	Denmark	45	97	0.9	0.5–1.6
Schoemaker et al., 2005 [14]	Denmark, Finland, Sweden, Norway, UK	360	1.934	0.9	0.7–1.1
Takebayashi et al., 2006 [19]	Japan	51	192	0.7	0.4–1.2
Klaboe et al., 2007 [51]	Norway	22	227	0.5	0.2–1.0
Schlehofer et al., 2007 [17]	Germany	29	74	0.7	0.4–1.2
Hours et al., 2007 [18]	France	58	123	0.9	0.5–1.6

The study was run from 1999 to 2004, with 678 cases and 3553 controls, and is the largest case-control study on the subject. It found no significant relation between cell-phone use and onset of neuroma, whether globally or in subgroups with high exposure in terms of duration of use or cumulative use (Fig. 1).

Neuromas, however, were significantly more frequently on the side of phone-use after 10 years' exposure ($n=23$; controls = 72; OR = 1.8; 95% CI, 1.1–3.1), although the authors attributed little importance to this barely significant finding.

Hardell et al. [28] (Fig. 2) reported a significantly increased risk of tumor associated with more than 10 years' (RR = 2.9; 95% CI, 1.6–5.5) or 1000 hours' (RR = 2.2; 95% CI, 1.4–3.4) cordless and/or cell-phone use. The proportion of tumors directly attributable to cordless or cell-phone use was 20.4% ($n=50$ cases; 95% CI, 13–77%). There was also a strong association between analogic phone use and acoustic neuroma, even with less than 500 hours' use.

Both studies involved methodological limitations.

In the INTERPHONE study, cell-phone use was defined broadly, as at least one call per week for at least 6 months,

and the subgroup of regular and longstanding users was small: only 127 or the 678 cases had used a cell-phone for more than 5 years in Shoemaker et al.'s report. Data were collected by interview, with a risk of influence and interpretation bias. The multicenter design, with a large number of interviewers, impaired homogeneity and thus statistical power. Control response rates were low, with less than 50% of preselected subjects finally included. Control subject selection criteria varied between countries (physicians' registers, public registers, etc.), again impairing power.

The type of phone (analogic or digital) was not recorded, and exposure to other similar electromagnetic fields (cordless DECT phones) was not taken into account.

In Hardell et al.'s study [24], subjects with more than 500 hours' use were few: 13 "analogic" and 22 "digital" cases; confidence intervals were thus wide, with marginal significance despite a high odds ratio.

Cases and controls were not matched geographically, and the high response rate suggests forced participation, with a risk of inexact or false replies.

Double exposure (cell and cordless phones) was not taken into account in risk calculation.

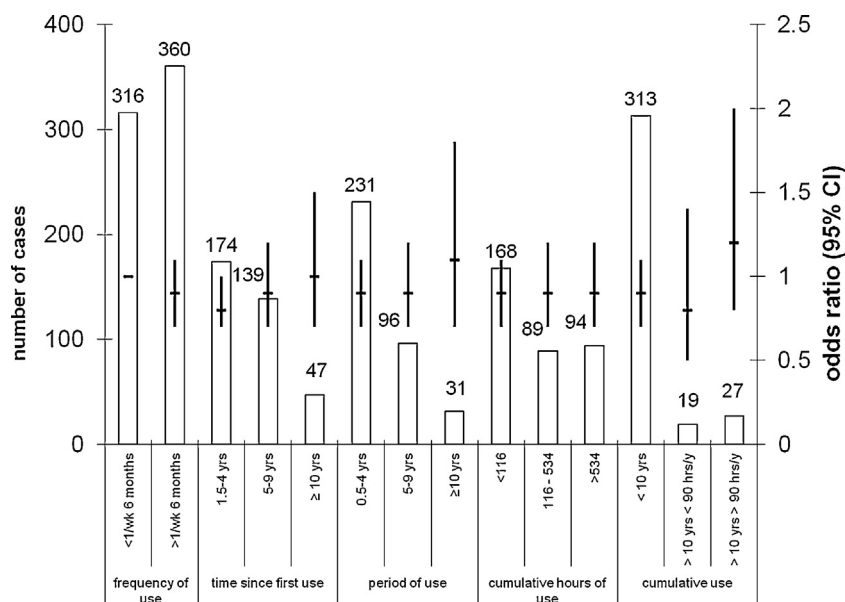


Figure 1 Partial results of the INTERPHONE study, from Denmark, Finland, Norway, UK and Sweden. Odds ratio and 95% confidence interval and numbers per exposure subgroup.

Schoemaker et al. [14]

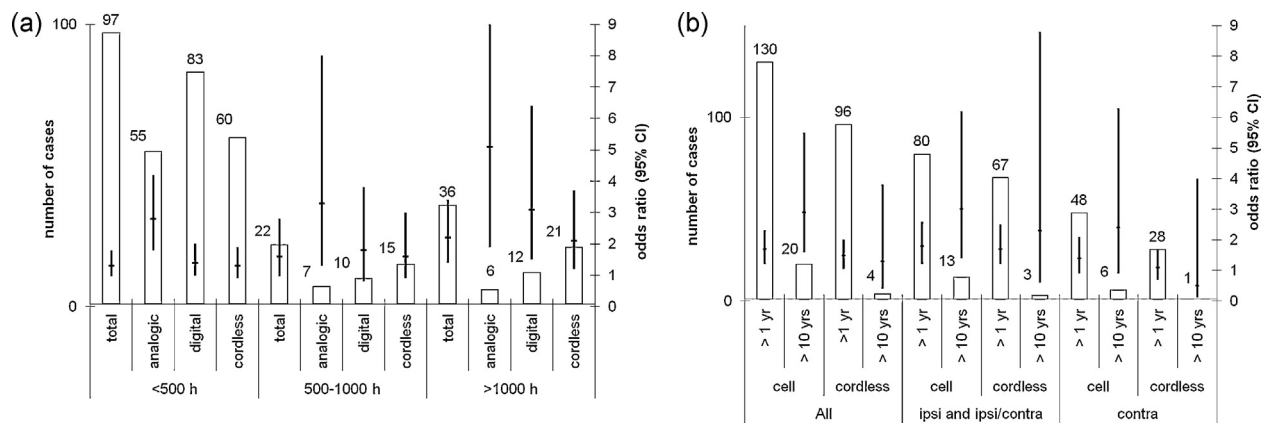


Figure 2 Results per user group: odds ratio, 95% CI and numbers.
Hardell et al. [28]

The results, moreover, were inconsistent. Risk was already significant with low exposure (<5 years) for analogic and digital mobile phones and for cordless phones. In subjects with less than 5 years' use, risk was higher with lower (<64 hours) than higher (>64 hours) use-level. Finally, the results pointed to a significant association between cell-phone use and contralateral tumor.

Meta-analyses

There were five meta-analyses.

The first part of Hardell et al.'s 2008 meta-analysis [35] (Tables 2 and 3) covered nine case-control studies comparing risk in users and non-users. The odds ratio showed no association between cell-phone use and acoustic neuroma.

The methodology took account of the lack of homogeneity in risk measurement, using a random effects model, since the definition of both user and exposure varied between studies.

The second part focused on subjects with more than 10 years' use. It covered four studies and found a barely significant risk (95% CI, 1.1–5.3) of ipsilateral neuroma after at least 10 years' cell-phone use.

Kan et al.'s 2008 meta-analysis [36] also used a random effects model. It excluded Hardell et al.'s data, on the grounds that including cordless phones (DECT) precluded homogeneity. Inskip et al.'s data were included, although, as pointed out above, the user group had very low risk exposure. Other studies were not included (INTERPHONE group). The risk assessed was global, regardless of laterality.

The authors concluded that no significant association obtained.

Khurana et al.'s 2009 meta-analysis [37] focused on the association between cell-phone use and neuroma after 10 years' exposure. The studies analyzed were the same as in Hardell et al.'s meta-analysis, but with a different methodology, using a fixed effect model requiring homogeneous measurements: i.e., identical theoretic odds

Table 2 Nine case-control studies of overall association between cell-phone use and vestibular schwannoma, with Hardell et al.'s meta-analysis [35].

Study, author, date, country	n cases	n controls	OR	95% CI
Inskip et al., 2001 [13], USA	40	358	0.8	0.5–1.4
Lönn et al., 2004 [16], Sweden	89	356	1	0.6–1.5
Christensen et al., 2004 [15], Denmark	45	97	0.9	0.5–1.6
Schoemaker et al., 2005 [14], Denmark, Finland, Sweden, Norway, Scotland, UK	360	1934	0.9	0.7–1.1
Hardell et al., 2006 [24], Sweden	130	900	1.7	1.2–2.3
Takebayashi et al., 2006 [19], Japan	51	192	0.7	0.4–1.2
Klaboe et al., 2007, Norway	22	227	0.5	0.2–1.0
Schlehofer et al., 2007 [17], Germany	29	74	0.7	0.4–1.2
Hours et al., 2007 [18], France	58	123	0.9	0.5–1.6
Meta-analysis	824	4261	0.9	0.7–1.1

OR: odds ratio; 95% CI: 95% confidence interval.

Table 3 Four case-control studies of association between cell-phone use exceeding 10 years and vestibular schwannoma, with Hardell et al.'s meta-analysis [35].

Study, author, date, country, latency	Total			Ipsilateral			Contralateral		
	<i>n</i> cases/ controls	OR	95% CI	<i>n</i> cases/ controls	OR	95% CI	<i>n</i> cases/ controls	OR	95% CI
Lönn et al., 2004 [16], Sweden ≥ 10 years	14/29	1.8	0.8–4.3	12/15	3.9	1.6–9.5	4/17		
Christensen et al., 2004 [15], Denmark ≥ 10 years	2/15	0.2	0.04–1.1	–/–	–	–	–/–	–	–
Schoemaker et al., 2005 [14], Denmark, Finland, Sweden, Norway, Scotland, UK ≥ 10 years	47/212	1	0.7–1.5	31/124	1.3	0.8–2.0	20/105	1	0.6–1.7
Hardell et al., 2006 [24], Sweden ≥ 10 years	20/99	2.9	1.6–5.5	10/28	3.5	1.5–7.8	6/29	2.4	0.9–6.3
Meta-analysis	83/355	1.3	0.6–2.8	53/167	2.4	1.1–5.3	30/151	1.2	0.7–2.2

OR: odds ratio; 95% CI: 95% confidence interval.

ratio; however, as pointed out above, these studies varied in user classification criteria, and cannot be considered homogeneous.

The conclusion was similar to Hardell et al.'s: a significant association between subjects with at least 10 years' cell-phone use and ipsilateral tumor.

Lahkola et al.'s meta-analysis [38] used much the same fixed effects methodology, and found no significant association.

Myung et al.'s meta-analysis [39] looked at the overall relation between cerebral tumor and cell-phone use. Using the Newcastle-Ottawa Scale (NOS) to assess case-control study quality in meta-analyses, the authors found a significant association between cell-phone use and cerebral tumor risk in low-bias studies; these were almost exclusively (7 out of 8) those by Hardell et al. A meta-analysis based on reports from a single team requires cautious interpretation: Myung et al. provided no specific findings in regard to acoustic neuroma, but did illustrate the difficulties of interpreting a meta-analysis.

Discussion

Various types of study have been published on the association between cell-phone use and vestibular schwannoma.

The registry studies fail to confirm or rule out a link, and merely rule out any major effect.

The more robust case-control studies (INTERPHONE and Hardell et al.) agree on the absence of association between less than 10 years' use of a digital phone and tumor onset. For periods exceeding 10 years' use, sample sizes were too small to demonstrate any clearly significant association, and the authors dispute the interpretation to be put on the data.

Finally, none of the five meta-analyses were methodologically rigorous or satisfactorily answered the question as to

a clinical link. Results were barely significant and founded on disparate studies.

In all, the case-control studies were the most informative, given the low incidence of vestibular schwannoma in the general population. The contradictory analyses founded on their results can be explained by limitations in interpretation due to their retrospective designs and the problems of measuring exposure.

Non-response has been shown to be a factor reducing odds ratios [40], and this may account for some of the discrepancy between the INTERPHONE studies, with low response rates, and those of Hardell et al., where response rates were high.

In these studies, cell-phone use was estimated retrospectively.

Assessment of call-time seems to be a good indicator of real phone use, according to Samkange-Zeeb et al. [41] and Funch et al. [42]. It remains, however, only an approximation, subject to memory bias. Hours et al. reported a reproducible discrepancy between real phone use (measured from operator data) and self-declared use [43]. The discrepancy is variable, increasing with level of use, but is already significant in retrospective assessment of less than 6 months' use, and weakened the power of Vrijheid et al.'s study [44]. Up to a 30% reduction in odds ratio was calculated for the INTERPHONE study.

Only one study [45] provided reliable data on the reliability of retrospective assessment of side of use in both healthy and vestibular schwannoma subjects: the latter, influenced by the diagnosis of tumor, tend to blame their cell-phone and to overestimate phone use on the affected side.

Significance levels in the case-control studies were low, and interpretation should bear in mind the approximate nature of the correlation between the results as reported and reality.

Electromagnetic field exposure is the physiopathological factor put forward to explain the possible oncogenic effects of cell-phone use. The cell phone is a cordless and mobile telecommunication system using radiocommunication between the relay antennae of the cell-phone network, with transmission to the landline network; it is thus a source of radioelectric waves (also called radio waves or Hertzian waves), creating a novel exposure of users to electromagnetic radiation.

The radioelectric waves used in telephone communication are low-frequency (300 MHz to 3 GHz) non-ionizing electromagnetic waves, the close field intensity of which is measured as the specific absorption rate (SAR). In cell-phones, the SAR is less than ≈ 2 W/kg, which is an infrathermal level (i.e., < 4 W/kg), as confirmed in *in vivo* assessment [46].

Two types of biological impact have been described for the electromagnetic radiation (300 MHz to 3 GHz) involved in cell-phones: thermal effects as of 4 W/kg and, controversially, non-thermal effects due to electromagnetic field exposure as such.

Most reports studied electromagnetic exposure in terms of phone use; none reported data for SAR. SAR, however, varies considerably from one phone to another and according to conditions of use (urban or rural). These variations in SAR have been quantified [47], with emission power varying 2- or 3-fold from one country to another under similar conditions of use.

None of the studies mentioned the model of cell-phone being used or its conditions of use—which once again testifies to the approximate nature of reported exposure assessments.

Conclusions and perspectives

The development of a tumor induced by a carcinogen requires repeated and lasting exposure to progressively overcome antitumor mechanisms. There is thus a minimum upstream exposure time before onset of any cell deregulation. Subsequently, there is then a period of latency, varying according to tumor evolution, before diagnosis. Schwannomas are slow growing. The combination of these two mechanisms accounts for the interval between exposure to a carcinogen (cigarette smoke, UV radiation, alcohol, asbestos, ionizing radiation, etc.) and tumor diagnosis. Conversely, tumor onset within 5 years of initial exposure is improbable.

Mass use of cell-phones is a recent phenomenon (in 1997, only 10% of the French population were active users), as is preponderant or exclusive use of cell-phones. There are thus few users with longstanding (> 10 years) intensive use, and it is not sure that a causal relationship can presently be demonstrated in such a population, even though cell-phone networks have been in existence for longer in certain countries, such as Japan and Sweden.

Moreover, reported results suffer from the retrospective nature of their exposure assessments and the lack of any long-term study.

Case-control studies should be continued as a watch program, to discover any link that may exist. Given, however, the rate at which cell-phone use has spread (reaching 80%

in France in 2008), control groups will soon be lacking, and with them any possibility of demonstrating a link.

Is a prospective study feasible? Low schwannoma incidence requires large-scale recruitment and the possibility of reliably and durably assessing individual exposure. The COSMOS study [48] was launched recently and is intended to follow up a cohort of 250,000 subjects in five northern European countries for a period of 25 years. Exposure will be measured from operator data. The main limitation of this ambitious project is that it, to be able to demonstrate any effect, it will require not less than a 3- to 7-fold elevation of risk of vestibular schwannoma. Moreover, data for side of use and SAR will be collected indirectly. This study would be capable of demonstrating a major effect of electromagnetic field, but will not be able to detect any risk less than 3 to 1.

The increase in the incidence of cerebral tumor [49] calls for exploration of environmental factors. Electromagnetic fields are one line of investigation, among many others, for clinical and epidemiological studies.

The study of the clinical impact of cell-phone use suffers presently from the lack of long-term follow-up in a large-scale population and of reliable quantification of exposure. Future studies will have to address these issues. Data on tumor size and evolutivity have seldom been provided, but could enable assessment of the infraclinical phase and of the possible implication of cell-phones in evolutivity of pre-existing tumors.

In the years to come, clinical studies will run up against the generalization of cell-phone use and exposure to other sources of radiation (Wi-Fi, bluetooth, etc.) that are difficult to measure. As the population of non-users virtually disappears, exposure assessment will have to be more precise if any effect is to be detected.

Only a long and costly cohort study will be able to reduce bias. Its results will be open to criticism, and not available until 2025–2030. What is to be done meanwhile? However imperfect, the first clinical studies should be enough to give the public reasonable reassurance as to the absence of any major effect. *In vitro* studies, moreover, have not shown any genotoxicity associated with electromagnetic fields [50].

Finally, it is to be borne in mind that no clinical studies have demonstrated an association between non-ionizing electromagnetic radiation exposure and any benign or malignant human pathology. Results from glioma studies have been discordant, and no syndrome of hypersensitivity to electromagnetic fields has been scientifically demonstrated.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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